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| 10/017,828 | 12/07/2001 | Keith Schappert | 50211/015003 | 6738 |

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| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/017,828 | SCHAPPERT, KEITH | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/19/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Priority*

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-15 of this application. The provisional application does not appear to provide specific basis for the negative proviso "non-Alzheimer's neurological disease." Since specific basis for this proviso is not present, the instant claims are not granted priority to the provisional application.

### *Claim Objections*

2. Claims 9 and 10 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims fail to further limit the independent claims since these all require that the GPIIIa gene encode a polypeptide with a proline at amino acid position 33 of SEQ ID NO: 4 (for claim 9) and that the GPIIb gene encode a polypepetide with a serine at amino acid position 843 of SEQ ID NO: 8 (for claim 10).

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 3 are all indefinite over the recitation "a non-Alzheimer's neurological disease consisting of Huntington's diseases, Parkinson's disease..." because it is not clear if applicant intends to imply that all of the particularly recited diseases are one umbrella disease (i.e. **a** non-Alzheimer's neurological disease) or if the method intends that the method of the claim be applied to one of the diseases selected from the list. Amendment of the claim to include language, for example, "a disease selected from the group consisting of" would overcome this rejections. All of the remaining claims are indefinite over this recitation because they all depend from one or all of these claims.

Claims 1, 2, and 3, are further indefinite over the second recitation of the phrase "the gene" because at the point in the claim where "the gene" is recited for the second time two genes have been previously recited and it is not clear to which applicant refers. Reference to the genes by name instead of writing "the gene" would help clarify the claims.

In claim 4, the recitation "said clinical trial" lacks proper antecedent basis in the claim as the claim relates to claims 1 and 2. The claim is multiply dependent from three different claims, and only one of these previously mentions a clinical trail. Furthermore, claim 4 is indefinite over the recitation "said genotype places" because it is not clear how a genotype can complete the active process step of placing a subject into a subgroup.

Claims 7 and 8 are confusing over the recitation "said genotype is T/C at nucleotide 192 of SEQ ID NO: 2" and "said genotype is T/G at nucleotide 2622 of SEQ ID NO: 2." With

regard to claim 7, the independent claims require that the assayed gene encode a proline at amino acid position 33 of SEQ ID NO: 4. In order for the gene to encode a proline, the nucleotide at position 192 of SEQ ID NO: 2 must be a C, therefore, it is not clear what it means within the scope of claims 1, 2, or 3 for the genotype to be a T/C at nucleotide 192. Furthermore, it is not clear what "said genotype is T/C at nucleotide 192" actually means because it is not clear if applicant is implying a heterozygote at position 192 or if applicant is implying that the nucleotide is a T or a C at position 192. Likewise, analogous problems exist with regard to claim 8 as it relates to the independent claims.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the Invention**

Independent claim 1 is drawn to a method for identifying a subject at risk for a non-Alzheimer's neurological disease comprising determining the genotype at nucleotide 192 of SEQ ID NO: 2 and/or determining the genotype at nucleotide 2622 of SEQ ID NO: 6, wherein said genotype is indicative of said subject having an increased risk for said non-Alzheimer's neurological disease. Thus, the nature of the invention requires the knowledge of an association

between SEQ ID NO: 2 and SEQ ID NO: 6 and the recited non-Alzheimer's neurological diseases such that the presence of particular alleles of these two genes is indicative a predisposition to one or all of these diseases.

Claim 2 is drawn to a method of diagnosing a subject, and comprises an identical determining step, wherein said genotype is indicative of said subject having said non-Alzheimer's neurological disease. The nature of the invention recited in claim 2 requires not only the knowledge of an association between the polymorphisms and the diseases, but it requires a higher level of knowledge such that the presence of particular alleles would be sufficient to conclude that a subject has a particular disease, as recited by the claim.

Claim 3 is drawn to a method for characterizing the genotype of at least one subject involved in a clinical trial of a gene therapy for the treatment of one of the recited non-Alzheimer's neurological diseases, and comprises only steps of determining the genotpye of the subject. There is no active process step which relates to the preamble, however the implication of the claim is that knowing the genotype of the subject will in some way be useful for the clinical trial. This implication is supported by dependent claim 11 which states that the genotype is indicative of the efficacy or therapeutic benefits of said therapy. Thus, in order to use the method of claim 3, like claims 1 and 2 the nature of the claimed invention requires knowledge of how the recited genotypes are related to any or preferably all of the recited diseases.

The remaining claims are dependent claims which further describe the methodology utilized to carry out the determining.

**Scope of the Claims**

The claims are broad in nature with regard to the range of non-Alzheimer's neurological diseases that are recited in the claims, including a diversity of diseases with a variety of etiologies and symptomatologies. The claims are limited to the screening of two particular polymorphisms.

**Level of Unpredictability and State of the Art**

The state of the art with regard to the association between a polymorphism and a trait is highly unpredictable.

Carlsson *et al.* (Stroke, July 1997, 28(7)1392-1395) tested polymorphisms of the human platelet antigens and found that they were not correlated with increased risk of stroke. In particular, Carlsson *et al.* examined the polymorphisms which are central to the instant claims, referred to therein as the HPA-1 and HPA-3 polymorphisms (p. 1392). Carlsson *et al.* state "Our results indicate that there is no correlation between the genotypes of the platelet receptor polymorphisms HPA-1, HPA-2, HPA-3, and HPA-5 and stroke." Likewise, Ridker *et al.* (The Lancet; Feb 1997; Vol. 349, p. 385-388) found that in a large cohort of apparently healthy men, carriage of the GPIIIa PIA1 allele was not associated with stroke (summary, p. 385, and throughout).

Even if an association is demonstrated between an allele and a particular polymorphism, the association might not be observed in other populations. Wagner *et al.* (Stroke, March 1998, 29(3)581-585) demonstrate this type of unpredictability in their study of the GPIIIa polymorphism and stroke in young women. Wagner *et al.* were not able to demonstrate any association between the entire population that they studied (which included black and white women) and stroke, but a further analysis demonstrated that the PIA2 polymorphism appeared to

be associated with stroke risk among white women. However, a priori, it was highly unpredictable which subset of the population would display an observable association.

Furthermore, the state of the art is unpredictable in that the art demonstrates multiple cases where an allele that was shown to be associated with Alzheimer's disease was not associated with a particular tested non-Alzheimer's neurological disease.

Marder *et al.* (Marder *et al.* Neurology 1994, July 44(7)1330-1331) teach that there was no association between the apolipoprotein ε4 allele and dementia in Parkinson's disease patients, even though such an association was hypothesized because this allele is a genetic risk factor for Alzheimer's disease. Likewise, Stengard *et al.* (Acta Neruol Scand 1995, 92:297-298) did not observe an association between apolipoprotein E alleles and vascular dementia, but did observe an association between the ε4 allele and Alzheimer's disease. In the post-filing date art, Kalman *et al.* (Neurobiology of Aging, 2000, Vol. 21, p. 555-558) did not observe an association between the apolipoprotein E alleles and Parkinson's disease, but did observe an association with Pick's disease. There was no way to predict, however, which of these diseases would have been associated with the polymorphisms. Thus, again, highlighting the highly unpredictable nature of this technology.

**Guidance in the Specification; Working Examples**

The specification does not establish a relationship between either of the two recited polymorphisms and any non-Alzheimer's disease. There are no working examples within the scope of these claims. The specification, in the examples shows an association between alleles of the GPIIIa and GPIIb polymorphisms and Alzheimer's disease. Regarding non-Alzheimer's diseases, the specification states, "because the underlying mechanism influenced by the variant

GPIIIa and/or variant GPIIb allele status is not disease-specific, the GpIIIa and/or GPIIb allele-status is suitable for making patient predictions for non-AD neurological diseases as well (p. 11, beginning at line 10)." The specification does not provide any evidence to support this conclusory statement.

The specification does not provide any guidance or working examples to guide one practicing the claimed invention as to the nature of the relationship between the two recited polymorphisms and the recited diseases. The specification does not provide any guidance or evidence of the broad applicability of the association between these polymorphisms and these diseases, or guidance as to which populations the associations might be valid in a predictive sense. The specification provides absolutely no guidance or teaching as to how these polymorphisms might be associated with "efficacy or therapeutic benefits" of a therapy.

**Level of Experimentation**

In such an unpredictable art, an extremely high level of experimentation would be required to practice the claimed invention, as any association to be relied upon for the practice of the claimed invention would have to be empirically determined via screening of patient and control populations. Since it is established in the prior art that this is an unpredictable field of endeavor, one would have to perform this experimentation for each disease recited in the claims in order to establish relationships between the diseases and the genotypes.

**Conclusion**

Thus, having considered each of these factors, and in view of the lack of guidance in the specification, the lack of a single working example within the scope of the claims, the lack of predictability in the art area, and the high level of experimentation required to establish

empirically observed relationships between disease and genotype, it is concluded that it would require undue experimentation to practice the claimed invention.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 5, 7, 9, 12, and 13 rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by Wagner *et al.* (Stroke, March 1998, 29(3)581-585).

As previously noted in this office action, the instantly pending claims are not being granted priority to the provisional application. Therefore, this reference is available under 102(b). This reference is also being applied under 102(a). In the event that applicant is able to establish priority to the provisional application, the 102(b) rejection will be withdrawn but the 102(a) rejection will remain.

Wagner *et al.* teach a method comprising the steps of determining the genotype at nucleotide 192 of the GPIIIa gene of SEQ ID NO: 2, wherein the gene encodes a polypeptide with a proline at amino acid position 33 of SEQ ID NO: 4 of said subject, wherein said genotype is indicative of said subject having an increased risk for said non-Alzheimer's neurological disease.

Wagner *et al.* teach the genotyping of the human GPIIIa polymorphism in exon 3 of the gene in patients with stroke and healthy control patients, wherein the genomic polymorphism

results in a leucine (allele P1A1) or a proline (allele P1A2) (p. 582). Wagner *et al.* teach that the P1A2 allele is associated with stroke risk among young white women (ABSTRACT, p. 583, first column). Thus, the teachings of Wagner *et al.* meet all of the structural limitations of claims 1 and 3. In particular with regard to claim 3, the preamble of the claim sets forth a purpose (intended use) for the claim but the preamble does is not structurally related to the required method steps. With regard to claim 5, Wagner *et al.* teach that the determining is carried out using a PCR assay followed by restriction analysis. The PCR assay utilizes primers which are nucleic acid molecules that specifically bind to a GPIIIa nucleic acid molecule. With regard to claim 7, the genotype analyzed by Wagner *et al.* is inherently a T or C polymorphism at nucleotide 192 of SEQ ID NO: 2. The instant specification teaches that the alleles of this polymorphism are referred to as P1A1/P1A2 (p. 1 of specification). With regard to claim 9, the P1A2 allele detected by Wagner *et al.* encodes a proline at amino acid position 33 of SEQ ID NO: 4. With regard to claim 12, Wagner *et al.* teach performing restriction enzyme digestion of an amplified product of a GPIIIa nucleic acid molecule using the enzyme MspI (p. 582, 1st column). With regard to claim 12, the amplified product is a polymerase chain reaction product and the nucleic acid molecule is a GPIIIa gene product as the sample was from genomic DNA (p. 582).

Thus, the teachings of Wagner *et al.* anticipate the instantly rejected claims.

9. Claims 3, 4, 5, 6, 7, 8, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Carlsson *et al.*

Carlsson *et al.* teach a method that comprises determining the genotype at nucleotide 192 of the GPIIIa gene of SEQ ID NO: 2, wherein the gene encodes a polypeptide with a proline at

amino acid position 33 of SEQ ID NO: 4 (p. 1393). The teachings of Carlsson *et al.* meet the limitations of independent claim 3 because, though the claim has a recited use in the preamble of the claim, it does not appear that the recited use has an effect on the recited method steps of the claim. With regard to claim 4, Carlsson *et al.* examine both of the recited positions in both genes, referred to therein as HPA-1 and HPA-3 polymorphisms (p. 1392). With regard to claims 5 and 6 Carlsson *et al.* utilize allele specific PCR, a method which requires the use of nucleic acid molecules that specifically bind GPIIIa and GPIIb molecules. With regard to claim 7 and 8 the polymorphism detected by Carlsson *et al.* is a T/C polymorphism in the case of GPIIIa and a T/G polymorphism in the case of GPIIa (p. 1392). With regard to claims 9 and 10, Carlsson *et al.* teach these amino acid changes (p. 1392).

Thus, the teachings of Carlsson *et al.* anticipate the rejected claims.

10. Claims 3, 5, 7, 9, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ridker *et al.*

Ridker *et al.* teach a method that comprises determining the genotype at nucleotide 192 of the GPIIIa gene of SEQ ID NO: 2, wherein the gene encodes a polypeptide with a proline at amino acid position 33 of SEQ ID NO: 4 and at nucleotide 2622 of the GPIIb gene of SEQ ID NO: 6, wherein the gene encodes a polypeptide with a serine at amino acid position 843 of said subject (p. 386). The teachings of Ridker *et al.* meet the limitations of independent claim 3 because, though the claim has a recited use in the preamble of the claim, it does not appear that the recited use has an effect on the recited method steps of the claim. With regard to claims 5 Ridker *et al.* utilize PCR to amplify GPIIIa nucleic acids, a method which requires the use of nucleic acid molecules that specifically bind GPIIIb molecules. With regard to claim 7 the

polymorphism detected by Ridker *et al.* is a T/C polymorphism in the case of GPIIIa (p. 386). With regard to claim 9, Ridker *et al.* the polymorphic allele taught by Ridker *et al.* inherently encodes a proline (p. 386). With regard to claim 12, Ridker *et al.* teach determining the genotype by performing restriction enzyme digestion of an amplified product of a GPIIIa nucleic acid using the enzyme MspI (p. 386). The GPIIIa nucleic acid molecule is a GPIIIa gene as it was amplified from genomic DNA (p. 386).

***Conclusion***

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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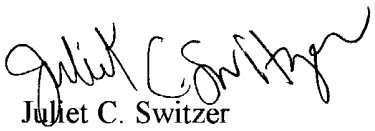

Juliet C. Switzer
Examiner
Art Unit 1634

September 6, 2004